Insulin and IGFs Enhance Hepatocyte Differentiation from Human Embryonic Stem Cells via the PI3K/AKT Pathway.

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Public Summary:
Human embryonic stem cells (hESCs) can be progressively differentiated into definitive endoderm (DE), hepatic progenitors and hepatocytes, and thus provide an excellent model system for the mechanistic study of hepatocyte differentiation, which is currently poorly understood. Here, we found that insulin enhanced hepatocyte differentiation from hESC-derived DE. Insulin activated the PI3K/AKT pathway, but not the MAPK pathway in the DE cells, and inhibition of the PI3K/AKT pathways by inhibitors markedly inhibited hepatocyte differentiation. In addition, IGF1 and IGF2 also activated the PI3K/AKT pathway in DE cells and their expression was robustly upregulated during hepatocyte differentiation from DE. Furthermore, inhibition of IGF receptor 1 (IGF1R) by a small molecule inhibitor PPP or knockdown of the IGF1R by shRNA attenuated hepatocyte differentiation. Moreover, simultaneous knockdown of the IGF1R and the insulin receptor (IR) with shRNAs markedly reduced the activation of AKT and substantially impaired hepatocyte differentiation. The PI3K pathway specifically enhanced the expression of HNF1 and HNF4 to regulate hepatocyte differentiation from DE. Although inhibition of the PI3K pathway was previously shown to be required for the induction of definitive endoderm from hESCs, our study revealed a positive role of the PI3K pathway in hepatocyte differentiation after the DE stage, and has advanced our understanding of hepatocyte cell fate determination.

Scientific Abstract:
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